

Theoretical Study of Cyclohexane -1,2-Diamine-Oxalate-Platinum Metal Complex and Comparing with Experimental Data: DFT Calculations

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Abstract

Theoretical studies for calculating the molecular structure and electronic properties of Cyclohexane -1,2-diamine-oxalate- platinum metal complex by using density functional theory (DFT) for get electronic properties and time dependent density functional theory (TD-DFT) for get excited state with B3LYP-SDD basis sets at the Gaussian 09 of programs. The electronic states of the system have been calculated depend on Koopmans' theorem.

The results showed that the excitation energies of oxaliplatinum lie in the UV region of electromagnetic radiation with very high biological reactivity, where The absorption spectra of complex recorded with wavelength (344.69nm), oscillator strength (0.0002). From calculations of the HOMO - LUMO energies, energy gap, hardness and softness, all this results showed oxaliplatinum are more soft and can easily interact with enzymes because the enzymes are big soft molecules. Thus, the optimized geometry shows a good agreement with the experimental results.

Keyword: Oxaliplatinum, B3LYP/DFT-SDD calculations, quantum chemical parameter and Enzymes.

Introduction

The basic components of cells picked by nature are metals ^[1]. In the enzyme catalytic domain, they are commonly located and are active in various biological processes, from electron exchange to catalysis and structural functions. They are commonly used in cellular activities ^[2].

Platinum coordination complexes have formed a new class of active anti-cancer agents in animals, and man, the most commonly studied compound, it's now in experimental clinical use against a wide range of human cancers^[3].

In the treatment of disease disorders, metal-based compounds have been commonly used. Platinum products, such as cis-platinum $\text{Pt}(\text{NH}_3)_2\text{Cl}_2$, carbo-platinum $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{Pt}$ and oxali-platinum $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_4\text{Pt}$ are the main of the metal-based compounds in the treatment of cancer ^[4]. Many metal complexes through, redesigning the current chemical structure by ligand substitution or constructing the entire new compound with improved protection, the synthesis has been synthesized. However, a handful of these drugs are currently under clinical trial due to increased focus on the clinical importance of metal-based complexes and several compounds are waiting to enter the trial.

Oxaliplatinum was discovered by Professor Yoshinori Kidani at the University of Nagoya City. Where, platinum compounds of the present generation were tested, in recent years, they have been focused on those with the 1,2-diaminocyclohexane carrier ligand,

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such as oxali-platinum.

The experiments molecular biology and in vitro cytotoxic screening by the National Cancer Institute find that diaminocyclohexane platinum, such as oxaliplatinum, belongs to a separate cytotoxic family, different from cisplatin and carboplatin [5].

Oxaliplatinum is a platinum compound that, mainly by inducing intrastrand cross-links in DNA [6].The

crystal structure of the drug oxaliplatinum anticancer compound consist of planar platinum(II) center binding with ligands 1,2 cyclohexane diamine, it also has oxalate group [7].

The formula for oxaliplatinum is [Pt (R, R-DACH) (oxalate)]. Fig.1 shows DACH are diaminocyclohexane and the formula of oxalate is CO_4^{2-} [8]. They bind together to form oxaliplatinum structure.

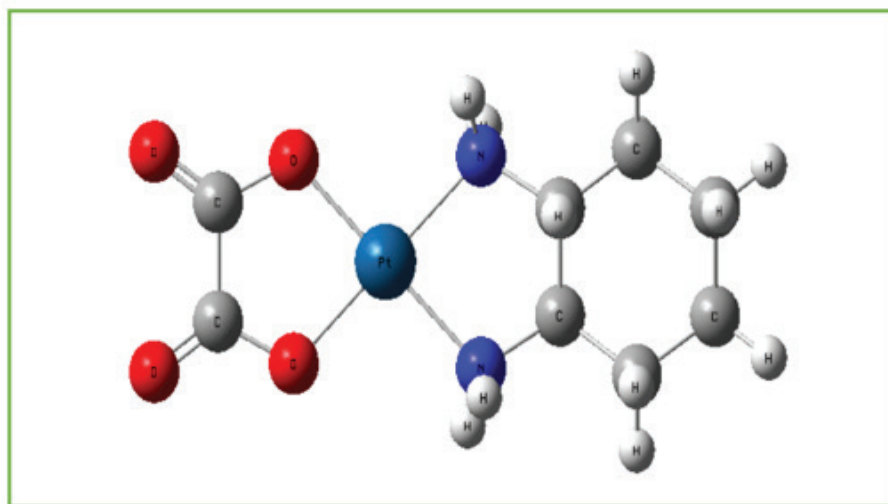


Fig.1: Geometrical structure cyclohexane-1,2-diamine-oxalate-platinum (oxaliplatinum)

Computational Details

In this study, the measurements were carried out. theoretically by using Gaussian 09 programs and Gauss View 5.0.8 program at the hybrid functional B3LYP together with SDD basis set possible quality for the system of interest for heavy metals use relativistic ECP, it is powerfully recommended for the heavy metals^[9]. DFT depends on the energy of the ground state and all other electrical properties of the ground state that are uniquely determined by the electron density ^[9-10]. Additionally, the exact ground state of the system corresponds to the electronic density for minimal total energy. TD-DFT which can be used to investigate the excited-state properties and dynamics of a system in the attendance of time-dependent. TD-DFT method has been verified to be effective in deciding the spectral properties of certain

transition metal complexes ^[11].

Results and discussion

The Cyclohexane-1,2-diamine-oxalate-platinum (oxaliplatinum), the structure is designed at Gaussian view 5.0.8. The resulting theoretical optimized parameters for the studied structure included bond length in angstrom \AA and bond angle in degree, seen in Table 1. The relaxation showed a suitable method is used to DFT-B3LYP/ SDD basis sets in our data theoretical framework are in good agreement with the experimental data ^[12-13].

When we compared our calculations with experimental data. One can see, the optimized bond lengths Pt-N, Pt-O, C-C, and C=O are approximately equal with experimental values in ref. ^[12]. While, bond

lengths are slightly larger than the experimental values in ref. ^[13]. Furthermore, much of the bond angles optimized are slightly larger than the experimental values.

Table 1: Bond lengths in Å and angles in degree of the oxaliplatinum.

Bond length (Å)	Our data theoretical	Expt. ^α	Expt. ^β	Bond Angle (deg.)	Our data theoretical	Expt. ^α	Expt. ^β
R(C-C)	1.57	1.53	1.19-1.50	A(C-C-C)	110.7- 111.6	111-111.4	106-113
R(C-N)	1.51	1.49	1.49	A(N-Pt-N)	83.5	82.4	83.8
R(Pt-N)	2.10	2.10	2.4-2.6	A(C-N-Pt)	109.1	108.6-109.3	106-107
R(Pt-O)	2.01	2.01	2.1-2.4	A(N-Pt-O)	96.42-179.6	96.8 -179.1	96-175.6
R(C-O)	1.36	1.34	1.21-1.32	A(Pt-O-C)	113.062	112.6	112-141
R(C=O)	1.23	1.22	1.29	A(O-C=O)	123.38	122.5	124
				A(C-C=O)	121.9	115.4	122
				A(C-C-N)	108.5- 113.6	108.1-113.9	107-105

^α from ref. ^[12].

^β from ref. ^[13].

Table 2 displays the Calculated outcomes of the total energy E_T (-843.0702914), E_{HOMO} , E_{LUMO} and Egap ($E_{LUMO} - E_{HOMO}$) of the oxaliplatinum. In contrast to that, we showed a strong agreement with experimental data ref.^[14], where listed in Table 2. Consequently, the present work is a suitable method a large separation was obtained between the valence and conduction bands. In our data, one can see LUMO energy (-1.1150658eV) greater than the HOMO energies (-5.852871), these results are similar to the result ref. ^[14]. The energy gap is a very important parameter as a symbol of the complexes biological reactivity, as can be seen in the table 2. Our Estimates, the Egap is 4.7378052eV in which the oxaliplatinum has insulating behavior. This outcome is in strong alignment with that of ref. ^[14], which corresponds to the high energy needed for oxaliplatinum

to donate or accept an electron.

Biological activity of metal complexes can determine through study quantum chemical parameter HSAB ^[15-16]. Table 2 gather the calculated values hardness H and softness S for the oxaliplatinum complexes, the Quantum Chemical Parameter Pattern depends on the coordination and the molecular geometry of the complexes. It is important to address with HSAB the coordination tendencies of complexes against the enzymes. Soft complexes have small energy gap and can easily interact with enzyme because the enzymes are big and soft molecules.

Hard complexes have large energy gap and more complex to interact with enzymes. thus, one can note the results under study through table 3 are in good agreement with those in ref ^[14]. Also, from table 2 declare the results of electronic properties for our data and experimental ref. 14.

The results showed the virial ratio ($-V/T = 2.1093$) lies in the same range for the molecular systems, this an indication to a suitable basis set used for the relaxation of the studied metal complex.

The ionization energy IE and electron affinity EA measured values revealed the results of our data using B3LYP-SDD basis sets are in good agreement with ref^[14]. Ionization potential and electron affinity demonstrate the vibrational behavior and they can be expressed in

terms of energies high molecular orbitals that are filled and low molecular orbitals that are unoccupied.

Ionization potential and electron affinity represents very important factors in symmetry, energy transfer and the stability of systems^[17-18]. IE equal to (5.852871eV) and EA equal to (1.1150658eV) stands for closed shell system and these results are corresponding to the large value of energy gap of the compound and it has insulating behavior.

Table 2: The HOMO, LUMO energies, I_E , E_A energy gap, virial ratio and quantum chemical parameter of the oxaliplatin.

Method	Our data	Reference[14]
EHOMO(eV)	-5.852871	-5.201032
ELUMO(eV)	-1.1150658	-0.4652528
Egap (eV)	4.7378052	4.7357792
ET(a.u)	-843.0702914	-842.906902
Hardness (e V)	2.3689026	2.3678896
Softness (e V)-1	0.211068197	0.211158493
$-\frac{V}{T}$	2.1093
IE(e V)	5.852871	5.201032
EA(eV)	1.1150658	0.4652528

Fig.2 reflects the distribution of the HOMO and LUMO molecular orbital maps for oxaliplatinum. Where,

A, B reflect present job, where red indicated negative regions with higher electronic density and green color indicated positive area.^[15] While C, D represent ref^[14], where red indicated negative regions and blue color indicate positive regions. In present work one can see, the distribution map is similar with experimental data ref^[14]. Where, the HOMO orbitals as an electron-donor

region and LUMO orbitals as an electron-acceptor region. The LUMO distribution of oxaliplatinum presents a p-antibonding orbital spread over the oxalate group, which constitutes a special electronic feature of oxaliplatinum. Thus, the compound can be acting as oxidant and reduced relatively.

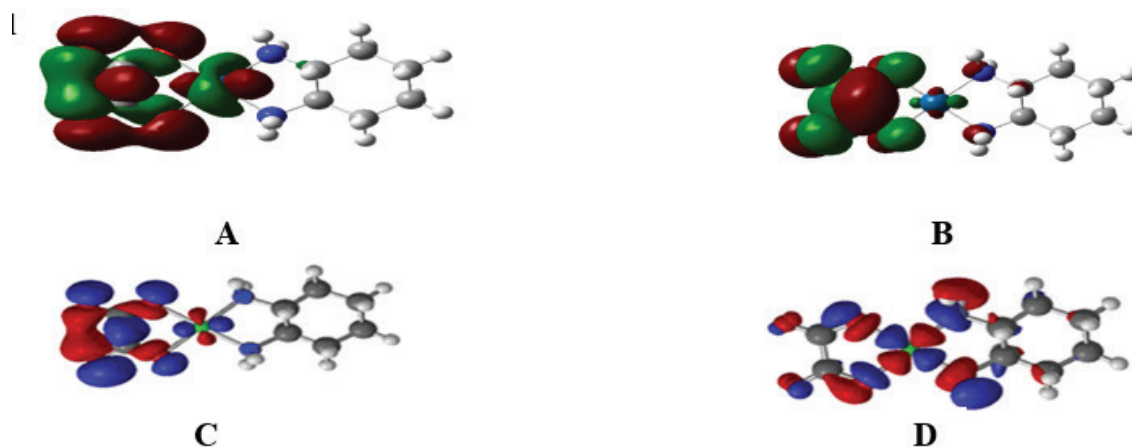


Fig.2: Distribution of the molecular orbitals (MOs)of the oxaliplatin maps: Present work HOMO(a) and LUMO(b). maps: Ref. [14] HOMO(c) and LUMO(d).



Fig. 3: The ESP distribution of the oxaliplatin (ESP Counter left and 3D ESP right).

Fig.3. illustrates the electrostatic potential ESP surfaces of Cyclohexane -1,2-diamine-oxalate- platinum Metal Complex by used to DFT-B3LYP/ SDD basis sets. Oxaliplatin ESP surfaces revealed that the potential was dragged into areas of high electronegativity. Thus, from figure 5 one can see

ESP demonstrates that, according to their mainly the high electronegativity, the charges are strongly dragged towards the oxalate group.

Excitation energy of the cyclohexane-1,2-diamine-oxalate-platinum metal complex was calculated by using the B3LYP-TD-DFT-SDD. The excitation energy of the main band appears at 3.597 eV, the oscillator strength, wave length, electronic transitions(HOMO→LUMO) and the transition characters were calculated and listed in Table 3.

Also, UV-Vis spectrum of oxaliplatin appears at (344.69 nm), one can note, the excitation energies lie in the UV region of electromagnetic radiation with very high biological reactivity.

Table 3: The excitation energy, oscillator strength, wave length, of the cyclohexane-1,2-diamine-oxalate-platinum metal complex was calculated by using the B3LYP-TD-DFT-SDD.

Excitation Energy (eV)	Oscillator Strength	Wave Length (nm)	Transitions HOMO→LUMO	Transition Character TC%
3.597	0.0002	344.69	H-3->L+1 HOMO->L+1 H-5->L+1 HOMO->L+3	10% 78% 6% 2%

Conclusion

After discusses the results of the structural and electronic properties of Cyclohexane -1,2-diamine-oxalate- platinum Metal Complex using B3LYP-SSD/ DFT, conclude the following:

- DFT/B3LYP-SDD basis sets used to study quantum chemical parameter and the electronic structure of the cyclohexane-1,2-diamine-oxalate-platinum (oxaliplatinum) metal complex.

- The result values of bonds and the angles are a good agreement with experimental data.

- Oxaliplatinum has insulating behavior due to E_g is wide between the valence and conduction bands. Thus, the great contribution to the construction of the molecular orbitals is due to the outer electrons with few contributions from the ligands in the platinum metal. Oxalate group consist of oxygen atoms have able to interact with the receptor reactive sites due to high their negative charge densities in which they are the most electronegative atomic sites in complexes.

- A good relaxation was obtained without any imaginary frequency for the studied structure.

- Oxaliplatinum has a low electronic softness value and requires high excitation energy to transfer electrons or to accept an electron.

- Absorption spectra of oxaliplatin with wavelength 344.69nm, in the UV region.

Conflict of Interest – Nil

Source of Funding- Self

Ethical Clearance – Not required

References

- [1] M. Frezza *et al.*, “Novel metals and metal complexes as platforms for cancer therapy,” *Curr. Pharm. Des.*, 2010, vol. 16, no. 16, pp. 1813–1825.
- [2] P. C. A. Bruijninx and P. J. Sadler, “New trends for metal complexes with anticancer activity,” 2008, *Curr. Opin. Chem. Biol.*, vol. 12, no. 2, pp. 197–206.
- [3] B. Rosenberg, “Noble metal complexes in cancer chemotherapy,” in *Inorganic and Nutritional Aspects of Cancer*, Springer, 1978, pp. 129–150.
- [4] M. Vojtek, M. P. M. Marques, I. M. Ferreira, H. Mota-Filipe, and C. Diniz, “Anticancer activity of palladium-based complexes against triple-negative breast cancer,” *Drug Discov. Today*, 2019, vol. 24, no. 4, pp. 1044–1058.
- [5] E. Raymond, S. G. Chaney, A. Taamma, and E. Cvitkovic, “Oxaliplatin: a review of preclinical and clinical studies,” *Ann. Oncol.* 1998, vol. 9, no. 10, pp. 1053–1071.
- [6] C. R. Culy, D. Clemett, and L. R. Wiseman, “Oxaliplatin,” *Drugs*, 2000, vol. 60, no. 4, pp. 895–924.
- [7] M. G. Apps, E. H. Choi, and N. J. Wheate, “The state-of-play and future of platinum drugs,” *Endocr Relat Cancer*, 2015, vol. 22, no. 4, pp. R219–R233.

- [8] T. C. Johnstone, "The crystal structure of oxaliplatin: a case of overlooked pseudo symmetry," *Polyhedron*, 2014, vol. 67, pp. 429–435.
- [9] A. C. Tsipis, "DFT flavor of coordination chemistry," *Coord. Chem. Rev.* 2014, vol. 272, pp. 1–29.
- [10] P. W. Abegg and T.-K. Ha, "Ab initio calculation of the spin-orbit coupling constant from gaussian lobe SCF molecular wavefunctions," *Mol. Phys* 1974, vol. 27, no. 3, pp. 763–767.
- [11] A. D. Laurent and D. Jacquemin, "TD-DFT benchmarks: a review," *Int. J. Quantum Chem.* 2013, vol. 113, no. 17, pp. 2019–2039.
- [12] P. Tyagi, P. Gahlot, and R. Kakkar, "Structural aspects of the anti-cancer drug oxaliplatin: A combined theoretical and experimental study," *Polyhedron*, 2008, vol. 27, no. 18, pp. 3567–3574.
- [13] M. A. Bruck, R. Bau, M. Noji, K. Inagaki, and Y. Kidani, "The crystal structures and absolute configurations of the anti-tumor complexes Pt (oxalato)(1R, 2R-cyclohexanediamine) and Pt (malonato)(1R, 2R-cyclohexanediamine)," *Inorganica Chim. Acta*, 1984, vol. 92, no. 4, pp. 279–284.
- [14] S.F.Teixeira *et al.*, "Evaluation of cytotoxic effect of the combination of a pyridinyl carboxamide derivative and oxaliplatin on NCI-H1299 human non-small cell lung carcinoma cells," *Biomed. Pharmacother.* 2016, vol. 84, pp. 1019–1028.
- [15] M. S. S. Adam, H. M. Abd El-Lateef, and K. A. Soliman, "Anionic oxide-vanadium Schiff base amino acid complexes as potent inhibitors and as effective catalysts for sulfides oxidation: Experimental studies complemented with quantum chemical calculations," *J. Mol. Liq.* 2018, vol. 250, pp. 307–322.
- [16] Faeq A. Al-Temimei and Hamid I. Abbood, "Density Functional Theory Calculations of Electronic Structure for Aluminum Metal Complexes", *Al-Bahir Quarterly Adjudicated Journal for Natural and Engineering Research and Studies*, 2019, Vol.10, No.19 and 20 p.(45-56).
- [17] Alaa S. Hussein, Zainab G. Abdulkareem and Hamid I. Abbood, "Electronic Structure of Suggested Nickel Metal Complexes: DFT Calculations", *NeuroQuantology*, 2020, Volume 18, Issue 8, pp. 33-39, NQ20202.
- [18] M. L. Jabbar, "Theoretical study for the interactions of Coronene-Y interactions by using Density functional theory with hybrid function," *Univ. Thi-Qar J.* 2018, vol. 13, no. 3, pp. 28–41.